Respiratory Medicine (2005) **99**, 1583–1590

ELSEVIER

respiratoryMEDICINE

Lung function in type 2 diabetes: the Normative Aging Study ☆

Augusto A. Litonjua[a,*], Ross Lazarus[a], David Sparrow[b,c], Debbie DeMolles[c], Scott T. Weiss[a]

[a]*Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115, USA*
[b]*Pulmonary Center, Boston University School of Medicine, 80 E. Concord St., Boston, MA 02118, USA*
[c]*VA Medical Center, 150 South Huntington Avenue Boston, MA 02130, USA*

KEYWORDS
Diabetes mellitus, type 2;
Blood glucose;
Longitudinal studies;
Epidemiology;
Respiratory function tests

Summary
Background: Cross-sectional studies have noted that subjects with diabetes have lower lung function than non-diabetic subjects. We conducted this analysis to determine whether diabetic subjects have different rates of lung function change compared with non-diabetic subjects.
Methods: We conducted a nested case-control analysis in 352 men who developed diabetes and 352 non-diabetic subjects in a longitudinal observational study of aging in men. We assessed lung function among cases and controls at three time points: Time0, prior to meeting the definition of diabetes; Time1, the point when the definition of diabetes was met; and Time2, the most recent follow-up exam.
Results: Cases had lower forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) at all time points, even with adjustment for age, height, weight, and smoking. In multiple linear regression models adjusting for relevant covariates, there were no differences in rates of FEV_1 or FVC change over time between cases and controls.
Conclusions: Men who are predisposed to develop diabetes have decreased lung function many years prior to the diagnosis, compared with men who do not develop

☆Grant Support:
1. KO8-HL03870 from the National Institutes of Health.
2. HL34645 from the National Heart, Lung, and Blood Institute.
3. A research Grant from Pfizer, Inc.
Dr. Litonjua is a recipient of an American Lung Association Research Grant.The Normative Aging Study is supported by the Cooperative Studies Program/ERIC of the U.S. Department of Veterans Affairs, and is a component of the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC).
*Corresponding author. Tel.: +1 617 525 0997; fax: +1 617 525 0958.
E-mail address: augusto.litonjua@channing.harvard.edu (A.A. Litonjua).

0954-6111/$ - see front matter
doi:10.1016/j.rmed.2005.03.023

diabetes. This decrement in lung function remains after the development of diabetes. We postulate that mechanisms involved in the insulin resistant state contribute to the diminished lung function observed in our subjects.

Introduction

Various lung function abnormalities have been described in type 1 diabetic subjects [reviewed in Sandler[1]]. For example, some type 1 diabetic subjects have reduced lung volumes, reduced elastic recoil, and reduced diffusing capacity. These observations have not been consistently confirmed possibly because of inadequate control of smoking in many of these studies. [1] Although few studies have been conducted in type 2 diabetic subjects, the weight of the evidence appears to point to lower lung function indices in these subjects compared with non-diabetic subjects. Furthermore, because the prevalence of diabetes is increasing, with type 2 diabetes accounting for 90–95% of all cases,[2] it is important to determine whether these lung function changes also occur in type 2 diabetes, since this may potentially have an impact on prognosis and disease management. Three cross-sectional studies have found lower lung function in subjects with type 2 diabetes compared with non-diabetic subjects,[3–5] whereas one did not find any difference.[6] However, the question of whether type 2 diabetic subjects have greater lung function declines compared with non-diabetic subjects remains unanswered. Clinical trials of inhaled insulin suggest that, at least in the very short term, diabetic subjects do not experience great changes in their lung function.[7,8] Only two studies from the same research group have reported longitudinal lung function changes in type 2 diabetic subjects. Lange et al.[9] found that subjects who developed diabetes during a 5-year period of follow-up had the steepest declines in lung function compared with non-diabetic subjects, whereas those who had diabetes at the beginning of the period of observation did not have significantly greater declines in lung function compared with non-diabetic subjects. Their follow-up study over 15 years did not detect any differences in lung function decline between diabetics and non-diabetics.[10]

In order to further clarify the relationship between diabetes and lung function, we conducted an analysis of lung function and lung function decline in a cohort of men who have participated in a longitudinal study of normal aging. The longitudinal nature of our cohort allowed us to examine the association between lung function and diabetes in the periods prior to, and after the recognition of the disease, and to compare the rates of change in lung function between diabetic subjects and non-diabetic subjects.

Methods

Population and study sample

The Normative Aging Study is a longitudinal study of aging established by the Veterans Administration in 1961.[11] The initial cohort of study subjects consisted of 2280 community-dwelling men from the Greater Boston area who were 21–80 years of age at the time of entry into the study between 1961 and 1969. Subjects were health screened at entry and were excluded if they had any antecedent chronic medical conditions, including hypertension, diabetes mellitus, heart disease, cancer, cirrhosis, peptic ulcer disease, gout, asthma, chronic bronchitis, or chronic sinusitis. Since entry, volunteers have reported for periodic examinations every 3–5 years, each consisting of a uniform medical history and physical examination, along with blood and urine tests, and spirometry. Details of this cohort have been published previously.[12,13] Participation in this study has been approved by the Human Studies Subcommittee of the Research and Development Committee, V.A. Medical Center, Boston, MA.

Study design and study sample

A nested case-control design was utilized. Cases and controls were selected from 1433 eligible subjects who had information regarding diabetes diagnosis, use of diabetic medications, and fasting blood glucose levels. Cases were defined as having diabetes if they met one or more of the following criteria: (1) A doctor's diagnosis of diabetes mellitus; (2) use of oral diabetic medication; (3) use of insulin; or (4) a fasting blood glucose of $\geqslant 7$ mmol/L. Controls were selected from among those with none of the above and a fasting blood glucose of <6.1 mmol/L, and were matched to cases by age (within 3 years) and date of exam at

which the case met the definition (within 1 year). Only subjects who had at least 3 exams with lung function data (at least one exam prior to meeting the case definition and at least one exam after meeting the case definition) were included in this analysis.

Three time points were identified for the analysis. The exam at which the subject met the case definition for diabetes was designated as T1. The earliest exam with lung function data prior to T1 was designated as T0, and the last exam after T1 was designated as T2. Two time periods were defined: T0–T1 was the period prior to recognition of diabetes, and T1–T2 was the period after.

Measurement of blood glucose

Blood glucose levels were measured after an overnight fast. From the beginning of the study through January 1970, serum glucose levels were determined by standard manual methods.[14] Thereafter, automated methods were used, with some changes over time in both the equipment (Technicon Auto-analyzer; Technicon Instruments Corp., Tarrytown, NY, from 1970 to 1973; Technicon AA II after 1973) and the specific assay used (the ferricyanide method, followed by a modified neocuproine method, and finally, the glucose oxidase method). Although these changes were not systematically evaluated at the time they were instituted, retrospective evaluation of the most important change, from manual to automated methods, suggested that glucose values were fairly consistent through this transition.[15]

Spirometry and lung function decline

Spirometry was performed in standard fashion as previously described[12,13] using a water-filled survey spirometer (Collins 8-L; Warren E. Collins, Braintree, MA, USA), and adhering to American Thoracic Society standards.[16] Each subject made up to eight forced vital capacity maneuvers to obtain three acceptable curves according to predefined criteria, and standard methods were used to obtain the forced vital capacity (FVC) and the forced expiratory volume in 1 s (FEV_1). The largest value of the three maneuvers for either measure (not necessarily from the same curve) was used for this analysis. All values were corrected to body temperature and pressure saturated with water vapor (BTPS).

Lung function change (ΔFEV_1/year and ΔFVC/year) was defined as lung function (in L for FEV_1 and FVC) at the beginning of the time period minus lung function at the end of the period, divided by the number of years between observations; thus, positive values correspond to a decline in lung function over time.

Statistical analysis

To assess the association of each variable with cross-sectional lung function (FEV_1, FVC, and FEV_1/FVC ratio, percent of predicted values) at each time point, univariate analyses were carried out utilizing *t*-tests for continuous variables and χ^2-tests for categorical variables. Multiple linear regression models for lung function were then fitted for each time point that included age, height, smoking status, and diabetes status. Because weight at each time point was different for the cases and controls, multiple linear regression models were also fitted which included weight to determine if this variable was associated with lung function differences among the cases and controls.

For lung function change, multiple linear regression models were fitted with FEV_1/year and FVC/year as the dependent variables. The independent variables included age at the beginning of the period, height, smoking status, and diabetes status. Separate multiple linear regression models were then fitted with weight and change in weight to determine if these were associated with lung function change. Additional models were fitted with baseline lung function level at the beginning of the relevant time period, in addition to the other variables described above. All analyses were conducted using the SAS statistical software package (SAS Institute, Inc., Cary, NC).

Results

Subject characteristics

A total of 352 cases and 352 controls were identified for this analysis. Among the cases, 195 men met the definition of a case by the fasting blood glucose criterion alone, while 157 cases were included for a combination of having elevated fasting blood glucose and a doctor's diagnosis ($n = 52$); having elevated fasting blood glucose and being on a diabetic medication ($n = 2$); and having all three criteria ($n = 103$). The median time of follow-up for T0–T1 was 13.6 years (range = 2.6–30.7 years), and for T1–T2 was 11.9 years (range = 2.0–29.8 years). Characteristics of the cases and controls are shown in Table 1. At time T0, prior to meeting the diabetes definition, age, height, and smoking status did not differ among

Table 1 Subject characteristics.

	T0			T1			T2		
	Cases ($n = 352$)	Controls ($n = 352$)	*P*-value	Cases ($n = 352$)	Controls ($n = 352$)	*P*-value	Cases ($n = 352$)	Controls ($n = 352$)	*P*-value
Age (years), mean ± SD	43.1 ± 8.1	43.2 ± 8.0	0.8	57.8 ± 8.4	57.7 ± 8.3	0.8	69.9 ± 7.2	69.8 ± 7.2	0.9
Height (m), mean ± SD	1.76 ± 0.06	1.75 ± 0.07	0.07	1.75 ± 0.06	1.74 ± 0.07	0.01	1.74 ± 0.06	1.72 ± 0.07	0.01
Weight (kg), mean ± SD	82.86 ± 10.82	77.45 ± 9.55	0.0001	86.64 ± 14.09	78.82 ± 10.90	0.0001	86.45 ± 14.73	79.23 ± 12.23	0.0001
Fasting blood glucose (mmol/L), mean ± SD	5.64 ± 0.49	4.67 ± 0.40	0.0001	6.61 ± 1.63	4.80 ± 0.37	0.0001	7.02 ± 2.42	4.74 ± 0.362	0.0001
Smoking status, *n* (%)									
Never	84 (23.9)	104 (29.5)		84 (23.9)	104 (29.5)		84 (23.9)	104 (29.5)	
Former	130 (36.9)	119 (33.8)	0.2	208 (59.1)	172 (48.9)	0.02	232 (65.9)	206 (58.5)	0.2
Current	138 (39.2)	129 (36.7)		60 (17.0)	76 (24.2)		35 (10.0)	42 (11.9)	

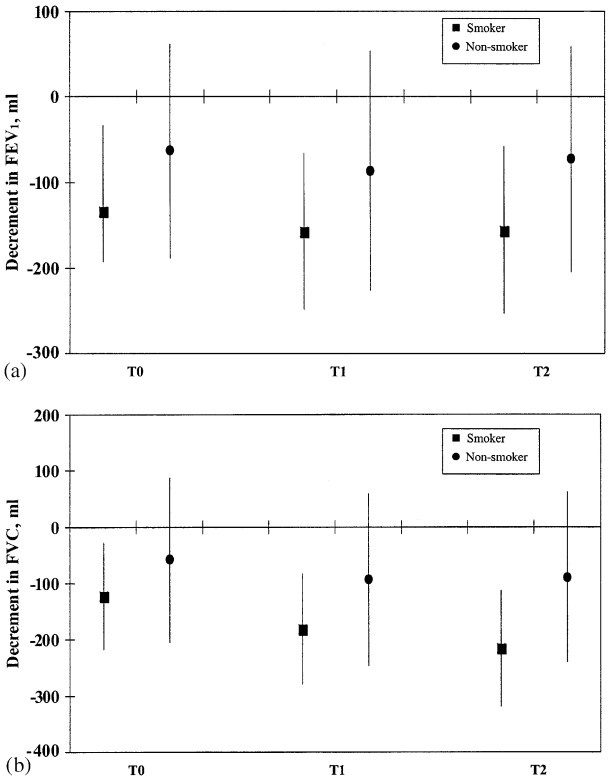

Figure 1 (a) Decrements in FEV_1 (in mL) among cases compared with controls at all time points, stratified by smoking status. Values are from β's and 95% CI obtained from linear regression models adjusted for age, height, and weight, and stratified by smoking status. (b) Decrements in FVC (in mL) among cases compared with controls at all time points, stratified by smoking status. Values are from β's and 95% CI obtained from linear regression models adjusted for age, height, and weight, and stratified by smoking status.

cases and controls. However, cases had higher fasting blood glucose levels and were also heavier than controls. At times T1 and T2, the differences between cases and controls with respect to fasting blood glucose and weight remained. At T1, smoking differed between cases and controls, largely due to the greater number of cases who switched from current smokers to former smokers, but this difference was not significant at T2.

Cross-sectional lung function analysis

Cases had significantly lower lung function values at all time points compared with controls, because smoking may confound the relationship between diabetes and lung function, we performed analyses stratified by smoking status. Because there were no significant differences among current and former

Table 2 Multiple linear regression models for lung function change/year.*

	T0–T1 β (SE)	*P*-value	T1–T2 β (SE)	*P*-value
ΔFEV_1: mL/year				
Intercept	−131.2 (55.5)	0.02	−86.2 (65.3)	0.2
Age	1.2 (0.2)	0.0001	0.6 (0.3)	0.02
Smoking status				
Never	—		—	
Current	9.7 (4.6)	0.03	11.8 (6.5)	0.07
Former	−0.3 (4.6)	0.9	3.0 (5.1)	0.6
Diabetic	1.1 (3.7)	0.8	1.1 (4.5)	0.8
Model R^2	0.10		0.07	
ΔFVC: mL/year				
Intercept	−206.3 (57.7)	0.0004	81.3 (63.7)	0.2
Age	1.4 (0.2)	0.0001	1.1 (0.3)	0.0001
Smoking status				
Never	—		—	
Current	12.6 (4.7)	0.008	14.6 (6.4)	0.02
Former	4.5 (4.8)	0.3	7.5 (4.9)	0.1
Diabetic	3.7 (3.8)	0.3	05.4 (4.4)	0.2
Model R^2	0.14		0.09	

*All models additionally adjusted for baseline height and weight.

smokers, we combined them into the group of ever smokers. In multiple linear regression models adjusting for age, height, and weight, cases were seen to have lower FEV_1 (Fig. 1(a)) and FVC (Fig. 1(b)) at all time points, however, these decrements only reached statistical significance among the ever smoking group.

Longitudinal lung function decline

Results of multiple regression models for change in lung function over time are shown in Table 2. There were no significant differences in yearly change in FEV_1 among cases and controls, for the two time periods of interest after adjustment for covariates. Based on the models in Table 2, subjects who developed diabetes only had about a 1.1 mL/year greater decline in FEV_1 compared with subjects who did not develop diabetes, both in the period prior to and after the recognition of diabetes. For yearly FVC change, cases had 3.7 and 5.4 mL/year greater declines compared with controls in the 2 periods of interest, respectively. When pack-years of smoking was substituted for smoking status in the models in Table 2, there results were unchanged. Additionally, we performed analyses stratified by smoking status but we did not find any significant decline in lung function among diabetics, whether or not they smoked.

Prior to meeting the definition of diabetes, aside from having greater baseline weight, cases had greater weight gain than controls: cases gained a mean ($\pm$SD) of 3.73 ($\pm$8.09) kg while controls gained 1.36 ($\pm$6.09) kg, $P<0.0001$. After meeting the case definition for diabetes, from T1 to T2, cases lost a mean of 0.18 ($\pm$6.68) kg and controls gained a mean of 0.41 ($\pm$6.09) kg, but this difference was not statistically significant ($P = 0.2$). When weight change for the particular period was substituted for baseline weight in the multiple regression models in Table 2, no changes in the effect of being diabetic on yearly lung function change was observed.

Discussion

This study on middle aged to older men confirms previous cross-sectional findings that lung function (FEV_1 and FVC, but not FEV_1/FVC ratio) in type 2 diabetic subjects is decreased compared with non-diabetic subjects, controlling for relevant covariates. This decreased lung function is present many years before the subjects are recognized as having diabetes mellitus. We also found that there is no

difference in yearly change in either FEV_1 or FVC between cases and controls, either in the period prior to recognition of diabetes or in the period after recognition of the disease.

Previous studies have also found diminished lung function among type 2 diabetic subjects. Both in the Copenhagen City Heart Study[3] and in the Fremantle Diabetes Study,[4] lung function among diabetic subjects was diminished when compared with lung function among controls. More recently, Walter et al.,[5] analyzed data on 3254 participants of the Framingham Offspring Cohort and found that both the diagnosis of diabetes and an elevated fasting blood glucose were associated with lower than predicted levels of pulmonary function. Similarly, a cross-sectional study of 3911 British women also found an association between low lung function and both a measure of insulin resistance and type 2 diabetes.[17] These decrements in lung function also appear to be present among children with established diabetes.[18] Our results confirmed these previous studies and found that lung function in diabetic subjects in our cohort was diminished when compared with non-diabetic subjects, even after adjusting for age, smoking status, height, and weight.

Our study documents diminished lung function many years (median time = 13.6 years) prior to the recognition of diabetes. Two recent studies from the same group[19,20] have also found that the risk for developing diabetes is inversely related to prior lung function. Additionally, it appears that low lung function among diabetics is also an independent predictor of all-cause mortality.[21] The decreased lung function observed in both type 1 and type 2 diabetic subjects has commonly been explained by the mechanism of glycosylation of proteins such as collagen in the lungs and chest wall,[22] the postulated process by which hyperglycemia leads to development of long-term diabetic complications in other organs.[23,24] This glycosylation results in irreversible collagen cross-linking, rendering the collagen less susceptible to proteolysis than native collagen, and leading to accumulation of collagen in lung connective tissue.[25] This process is likely to be chronic, and may occur even in non-diabetic subjects who have hyperglycemia.[3] However, this glycosylation process occurs in the early stages of diabetes when hyperglycemia is most pronounced and may decelerate, reaching a new equilibrium at a lower turn-over rate of collagen.[9,22] Thus, while this mechanism may explain the greater decrement in lung function in diabetic subjects seen around the time of their diagnosis as reported by Lange et al.,[9] it does not fully explain the diminished lung function of our cases at T0, many years prior to becoming diabetic, where the level of glycemia among cases was only mildly elevated when compared with controls (Table 1). Another potential mechanism that may explain the findings of decreased lung function is decreased muscle strength in diabetic subjects. In a previous analysis on this cohort,[26] we had shown that decreased skeletal muscle weakness (as measured by handgrip strength) was associated with an insulin resistant state. This decreased muscle strength was present many years prior to the recognition of the insulin resistant state.

It is known that at least three factors determine lung function at a particular point in adult life: (1) the maximally attained level of lung function; (2) the onset of decline of lung function (or alternatively, the duration of the plateau phase); and (3) the rate of decline of lung function[27] (21). It is generally accepted that lung function reaches a peak sometime around the ages of 20 and 25 years.[28,29] In healthy, non-smoking individuals, a phase follows wherein there is little or no change in lung function (the plateau phase),[30,31] although lung function can continue to increase into the fourth decade.[27,29] This plateau phase likely lasts until the ages of 30–35 years for most people,[29,30] after which a period of lung function decline ensues. Thus, since the mean age of our cases at T0 was 43.1 ± 8.1 years, it is likely that the diminished lung function among cases at T0 was due to either a lower maximally attained lung function or a lack of a plateau phase. We, therefore, postulate that other mechanisms, in addition to glycosylation of collagen, may be operating. It is conceivable that these subjects may be predisposed to developing both low lung function and diabetes. In prior analyses on non-diabetic subjects in our cohort, we found that lower lung function was associated with a state of insulin resistance (as measured by fasting insulin levels and the fasting insulin resistance index), both longitudinally[32] and cross-sectionally.[33] The finding by Lange et al.[3] of an inverse relationship between fasting glucose levels and lung function among non-diabetic subjects is also consistent with this. Furthermore, the cellular mechanisms underlying the insulin resistant state may also explain the observed relationship between low lung function with either cardiovascular disease[34–36,40] or all-cause mortality[21,37] in many epidemiologic studies.

While the exact mechanisms by which a state of insulin resistance leads to low lung function remains to be elucidated, it is becoming recognized that two hormones that may be involved in pathways of insulin resistance and glucose intolerance states—leptin and resistin—may have effects on

pulmonary mechanics[38] and airway inflammation.[39,41,42] As more research into insulin resistance states uncover these complicated pathways, it is likely that mechanisms to explain epidemiologic findings such as ours will come to light.

In this analysis, we controlled for covariates that have been known to affect lung function level, such as age, height, and cigarette smoking, and we also controlled for weight. However, as with many epidemiologic studies, residual confounding of these variables, in particular smoking, may affect the results. Thus, we conducted our analyses stratified by smoking status. Diabetics who were lifelong non-smokers had lower lung function at all time points compared with controls (Fig. 1(a) and (b)), although this did not reach statistical significance after controlling for covariates, because of the small sample size. Cases who were ever-smokers, on the other hand, had significantly lower lung function than ever-smoking controls, suggesting that there may be an interaction between smoking and the propensity for diabetes. When we tested for interactions between smoking and diabetes, however, we did not find a significant interaction (all P values for interaction > 0.05), and this may have been due to the lack of power in our study. Nevertheless, this might be an avenue for future studies in cohorts with adequate numbers of smoking and non-smoking diabetics.

A selection bias may arguably explain our results, wherein only the most healthy subjects who were at risk for diabetes completed the lung function testing, thus showing no differences in lung function declines over time compared with non-diabetic subjects. A review of our subject selection showed that 439 subjects met the diabetes criteria at some point during their follow up in the cohort. Twenty-five (5.7%) of these 439 were excluded because they met the criteria at the time of entry, three (0.7%) had no lung function data at all, 39 (8.9%) met the diabetes criteria at their last follow-up visit, and 20 (4.6%) subjects met the criteria, but there were no controls that could be matched to them. In all, 87 subjects were excluded, and a comparison of their characteristics and available lung function data with the 352 diabetic subjects who were in the study showed no significant differences (data not shown). Thus, although we cannot entirely rule this out, it is unlikely that selection bias could have played a large role in our study.

We did not find a significantly different yearly change in FEV_1 nor FVC among diabetic subjects compared with controls, either before or after being recognized as diabetic subjects. We used linear regression modeling in our analyses. When we performed a repeated measures analysis incorporating all the lung function observations between T0 and T2, we obtained almost identical estimates for the change in lung function among diabetics. Our results are also consistent with the only other longitudinal study of lung function in type 2 diabetes, which used random effects modeling and which followed both diabetics and non-diabetics for 15 years and did not find a difference in their rates of decline in lung function. Because of the small numbers in subgroups, we were unable to perform any meaningful analyses of the effect of treatment (i.e. insulin vs. oral hypoglycemic drugs) on the decline in lung function.

There is some controversy regarding the need to control for baseline level of lung function when investigating the rate of change in these parameters. We present our analyses without controlling for baseline lung function. When we controlled for baseline level, the parameter estimates (β) for ΔFEV_1/year increased to 0.0039 ($P = 0.3$) and 0.0055 ($P = 0.2$) for T0–T1 and T1–T2, respectively, but retained non-significant P-values. The parameter estimates for ΔFVC/year increased to 0.0067 ($P = 0.07$) and 0.0098 ($P = 0.02$) for the 2 time periods of interest, when we controlled for FVC at the beginning of the respective time periods. However, since both lung function parameters were significantly different between cases and controls at both T0 and T1, it is likely that these increased estimates for lung function declines, when control for baseline lung function is done, represent the phenomenon of regression to the mean.[40] In any event, the magnitude of these declines, even for ΔFVC/year, remains small and of uncertain clinical significance in this population.

In summary, subjects who are destined to develop diabetes have lower FEV_1 and FVC values many years prior to becoming diabetic, compared with age-matched subjects who do not develop diabetes. However, we did not find any differences in FEV_1 declines between diabetic subjects and controls. We postulate that mechanisms involved in the insulin resistant state may be responsible for predisposing individuals to a lower maximal attained lung function or to an early initiation of the decline in lung function.

References

1. Sandler M. Is the lung a "target organ" in diabetes mellitus? *Arch Internal Med* 1990;**150**:1385–8.
2. Williamson DF, Vinicor F, Bowman BA. Centers for Disease Control and Prevention Primary Prevention Working Group.

Primary prevention of type 2 diabetes mellitus by lifestyle intervention: implications for health policy. *Ann Internal Med* 2004;**140**:951–7.
3. Lange P, Groth S, Kastrup J, et al. Diabetes mellitus, plasma glucose and lung function in a cross-sectional population study. *Eur Respir J* 1989;**2**:14–9.
4. Davis TME, Knuiman M, Kendall P, et al. Reduced pulmonary function and its associations in type 2 diabetes: the Fremantle Diabetes Study. *Diab Res Clin Prac* 2000;**50**:153–9.
5. Walter RE, Beiser A, Givelber RJ, et al. Association between glycemic state and lung function: the Framingham Heart Study. *Am J Respir Crit Care Med* 2003;**167**:911–6.
6. Barrett-Connor E, Frette C. NIDDM, impaired glucose tolerance, and pulmonary function in older adults: the Rancho Bernardo Study. *Diab Care* 1996;**19**:1441–4.
7. Skyler JS, Cefalu WT, Kourides IA, et al. Efficacy of inhaled human insulin in type 1 diabetes mellitus: a randomized proof-of-concept study. *Lancet* 2001;**357**:331–5.
8. Cefalu WT, Skyler JS, Kourides IA, et al. Inhaled human insulin treatment in patients with type 2 diabetes mellitus. *Ann Internal Med* 2001;**134**:203–7.
9. Lange P, Groth S, Mortensen J, et al. Diabetes mellitus and ventilatory capacity: a five year follow-up study. *Eur Respir J* 1990;**3**:288–92.
10. Lange P, Pamer J, Schnohr P, Jensen G. Copenhagen City Heart Study: longitudinal analysis of ventilatory capacity in diabetic and nondiabetic adults. *Eur Respir J* 2002:1406–12.
11. Bell B, Rose CL, Damon D. The Normative Aging Study: an interdisciplinary and longitudinal study of health and aging. *Aging Hum Dev* 1972;**3**:5–17.
12. Sparrow D, O'Connor GT, Colton T, et al. The relationship of nonspecific bronchial responsiveness to the occurrence of respiratory symptoms and decreased levels of pulmonary functions. The Normative Aging Study. *Am Rev Respir Dis* 1987;**135**:1255–60.
13. O'Connor G, Sparrow D, Taylor D, et al. Analysis of dose-response curves to methacholine. An approach suitable for population studies. *Am Rev Respir Dis* 1987;**136**:1412–7.
14. Folin O, Wu H. A system of blood analysis. Supplement 1. A simplified and improved method for determination of sugar. *J Biol Chem* 1920;**41**:367–74.
15. Cassano PA, Rosner B, Vokonas PS, et al. Obesity and body fat distribution in relation to the incidence of non-insulin-dependent diabetes mellitus. A prospective cohort study of men in the Normative Aging Study. *Am J Epidemiol* 1992;**136**:1474–86.
16. American Thoracic Society. Standardization of spirometry—1987 update. Am Rev Respir Dis 1987; 136:1285–98.
17. Lawlor DA, Ebrahim S, Davey Smith G. Associations of measures of lung function with insulin resistance and type 2 diabetes: findings from the British Women's Heart and Health Study. *Diabetologia* 2004;**47**:195–203.
18. Cazzato S, Bernardi F, Salardi S, et al. Lung function in children with diabetes mellitus. *Pediatr Pulmonol* 2004;**37**:17–23.
19. Engström G, Janzon L. Risk of developing diabetes is inversely related to lung function: a population-based cohort study. *Diabet Med* 2002;**19**:167–70.
20. Engström G, Hedblad B, Nilsson P, Wollmer P, Berglund G, Janzon L. Lung function, insulin resistance and the incidence of cardiovascular disease: a longitudinal cohort study. *J Internal Med* 2003;**253**:574–81.
21. Davis WA, Knuiman M, Kendall P, Grange V, Davis TME. Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care* 2004;**17**:752–7.
22. Cavan DA, Parkes A, O'Donnell MJ, Freeman W, Cayton RM. Lung function and diabetes. *Respir Med* 1991;**85**:257–8.
23. Kohn RR, Schnider SL. Glucosylation of human collagen. *Diabetes* 1982;**31**:47–51.
24. Brownlee M, Vlassara H, Cerami A. Nonenzymatic glycosylation and the pathogenesis of diabetic complications. *Ann Internal Med* 1984;**101**:527–37.
25. Ofulue F, Thurlbeck WM. Experimental diabetes and the lung. II. In vivo connective tissue metabolism. *Am Rev Respir Dis* 1988;**138**:284–9.
26. Lazarus R, Sparrow D, Weiss ST. Handgrip strength and insulin levels: Cross-sectional and prospective associations in the Normative Aging Study. *Metabolism* 1997;**46**:1266–9.
27. Weiss ST, Ware JH. Overview of issues in the longitudinal analysis of respiratory data. *Am J Respir Crit Care Med* 1995;**154**:S208–11.
28. Kerstjens HAM, Rijcken B, Schouten JP, et al. Decline of FEV_1 by age and smoking status: facts, figures, and fallacies. *Thorax* 1997;**52**:820–7.
29. Knudson RJ, Lebowitz MD, Holberg CJ, et al. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983;**127**:725–34.
30. Tager IB, Segal MR, Speizer FE, et al. The natural history of forced expiratory volumes. Effect of cigarette smoking and respiratory symptoms. *Am Rev Respir Dis* 1988;**138**:837–49.
31. Sherrill DL, Lebowitz MD, Knudson RJ, et al. Smoking and symptom effects on the curves of lung function growth and decline. *Am Rev Respir Dis* 1991;**144**:17–22.
32. Lazarus R, Sparrow D, Weiss ST. Baseline ventilatory function predicts the development of higher levels of fasting insulin and fasting insulin resistance index: the Normative Aging Study. *Eur Respir J* 1998;**12**:641–5.
33. Lazarus R, Sparrow D, Weiss ST. Impaired ventilatory function and elevated insulin levels in nondiabetic males: the Normative Aging Study. *Eur Respir J* 1998;**12**:635–40.
34. Friedman G, Klatsky A, Siegelaub M. Lung function and risk of myocardial infaction and sudden cardiac death. *N Engl J Med* 1976;**294**:1071–5.
35. Kannel W, Hubert H, Lew E. Vital capacity as a predictor of cardiovascular disease: the Framingham study. *Am Heart J* 1983;**105**:311–5.
36. Lange P, Nyboe J, Jensen G, et al. Ventilatory function impairment and risk of cardiovascular death and of fatal or non-fatal myocardial infarction. *Eur Respir J* 1991;**4**:1080–7.
37. Neas LM, Schwartz J. Pulmonary function levels as predictors of mortality in a national sample of US adults. *Am J Epidemiol* 1998;**147**:1011–8.
38. O'Donnell CP, Tankersley CG, Polotsky VP, et al. Leptin, obesity, and respiratory function. *Respir Physiol* 2000;**119**:173–80.
39. Loffreda S, Yang SQ, Lin HZ, et al. Leptin regulates proinflammatory immune responses. *FASEB J* 1998;**12**:57–65.
40. Gomez-Ambrosi J, Frübeck G. Do resistin and resistin-like molecules also link obesity to inflammatory diseases? *Ann Internal Med* 2001;**135**:306–7.
41. Holcomb IN, Kabakoff RC, Chan B, et al. FIZZ1, a novel cysteine-rich secreted protein associated with pulmonary inflammation, defines a new gene family. *EMBO J* 2000;**19**:4046–55.
42. Schouten JP, Tager IB. Interpretation of longitudinal studies. An overview. *Am J Respir Crit Care Med* 1996;**154**:S278–84.